Psychiatric Times May 01, 2001

Investigating SAM-e for Depression

http://www.psychiatrictimes.com/articles/investigating-sam-e-depression

For more than eight years, Richard P. Brown, M.D., associate professor of clinical psychiatry at Columbia University College of Physicians and Surgeons, has used the natural dietary supplement S-adenosylmethionine (SAM-e) to treat more than an estimated 400 patients suffering from depression, many of whom were treatment-resistant. This month, Brown is scheduled to discuss SAM-e at the American Psychiatric Association's annual meeting in New Orleans.

Brown also has co-authored the book *Stop Depression Now: SAM-e, the Breakthrough Supplement that Works as Well as Prescription Drugs in Half the Time...With No Side Effects.* His primary collaborator on the book project was Teodoro Bottiglieri, Ph.D, director of neuropharmacology and senior research scientist at Baylor University's Institute for Metabolic Disease. Bottiglieri, also an associate professor of biomedical studies at Baylor, has been conducting research on SAM-e for 15 years.

In an interview with *Psychiatric Times,* Brown reviewed research on SAM-e and discussed his clinical experience with it.

Although SAM-e has only been on the U.S. market since 1999, it has been studied for decades internationally and is approved as a prescription drug in Spain, Italy, Russia and Germany. More than 1 million Europeans have used it, primarily for depression and arthritis.

"I first heard about SAM-e 20 years ago when I was doing my residency in psychiatry at New York Hospital, Cornell Medical Center," Brown recalled. "At a meeting of the American College of Neuropsychopharmacology, a colleague had learned about an exciting new antidepressant being studied in Europe that was nontoxic, without side effects, and worked better and faster than traditional medications."

Fifteen years later, after Brown had developed a subspecialty practice treating patients resistant to conventional drug therapy by integrating alternative approaches such as nutrients and herbs with prescription medications, a patient brought him information about SAM-e from the Internet. That launched his investigation and clinical use of SAM-e.

SAM-e was discovered in Italy about four decades ago (Cantoni, 1952), according to Brown. Since then, SAM-e "has been evaluated for various disorders in more than 75 clinical trials

involving over 23,000 people," Brown said. However, the first clinical study of SAM-e's use for depression was not completed until the 1970s (Agnoli et al., 1976).

"Because there was no usable oral preparation [then], early studies used intravenous [IV] and intramuscular [IM] formulations," Brown said. "Over time, improvements have provided an oral form that is much more resistant to oxidation and gastric enzyme degradation."

Biochemistry

Brown explained that SAM-e is produced in the body from methionine, a sulfur-containing amino acid, and the energy-producing compound adenosine triphosphate. SAM-e is a physiologically essential compound, he said, adding that some chemists believe it ranks with adenosine triphosphase (ATP) as a pivotal molecule in living cells. Distributed throughout the body, SAM-e is most concentrated in the brain and liver and is crucial to three central pathways of metabolism that stimulate more than 35 different reactions.

"The three major pathways are transmethylation, transulfuration and transaminopropylation," he said. "Animal studies show that the transmethylation pathway boosts levels of the neurotransmitters serotonin, dopamine and norepinephrine. This process probably contributes to the antidepressant action" (Andreoli et al., 1978; Curcio et al., 1978; Czyrak et al., 1992; Fava et al., 1990; Losada and Rubio, 1989; Otero-Losada and Rubio, 1989).

Brown said that donation of carbon groups by SAM-e protects catecholamine neurons and that SAM-e improves nerve cell membrane uptake of phospholipids, enabling the coupling of protein receptors to second messengers within a more fluid lipid bilayer and enhancing transmission of impulses by neurons.

"SAM-e is vital to the production of our most important antioxidant, glutathione, as well as the secondary antioxidants, cysteine and taurine," he noted. "The American diet yields insufficient quantities of SAM-e either for wellness or treatment of illness. Moreover, the form of SAM-e found in food is not stable. It oxidizes too rapidly to absorb well. Our bodies can only generate a small amount of SAM-e...Therefore, SAM-e levels are most easily increased through dietary supplementation."

Reviewing the Literature

According to Brown, lower than normal levels of SAM-e are found in cerebral spinal fluid in some patients with depression, Alzheimer's disease, dementia, Parkinson's disease treated with levodopa (Atamet, Sinemet), disorders of folate metabolism and other illnesses (Bottiglieri et al., 1990; Bottiglieri et al., 1994).

He cited a study indicating that folate, B12 and B6 are necessary for efficient use of SAM-e (Crellin et al., 1993) and reported that SAM-e has been effective for treating major depressive disorder in 13 trials comparing it to placebo and 19 trials comparing it to tricyclic antidepressants, with more than 1,400 patients studied.

"From 1973 to 1988, 14 double-blind, European studies [Janicak et al., 1988] showed that intravenous and intramuscular preparations of SAM-e were more effective than placebo and

comparable to imipramine [Tofranil], amitriptyline [Elavil, Endep] and clomipramine [Anafranil] for treatment of major depression," he said.

In 1988, American psychopharmacologists Bell and colleagues conducted a double-blind, randomized, two-week trial comparing IV SAM-e to oral imipramine. By the end of the second week, 66% of the S-adenosylmethionine patients "had a clinically significant improvement in depressive symptoms, compared to 22% of the imipramine patients," the study authors reported.

Since 1988, double- and single-blind studies using higher doses of SAM-e have shown it to be effective in treating major depression (Bressa, 1994; Delle Chiaie and Boissard, 1997; Delle Chiaie et al., 2000), depression secondary to medical illness (Criconia et al., 1994), postpartum depression (Cerutti et al., 1993), postmenopausal depression (Salmaggi et al., 1993) and treatment-resistant depression (Rosenbaum et al., 1990), Brown reported.

"Rapid response to SAM-e was shown in a double-blind trial of 30 depressed inpatients who received either 1600 mg/day of oral SAM-e or imipramine (averaging 140 mg/day) for six weeks," Brown added. "The SAM-e group was significantly better by day 10. Both groups were comparably improved by week 6" (De Vanna and Rigamonti, 1992).

Furthermore, Brown reported that in a small, double-blind, four-week inpatient study of oral SAM-e (1600 mg/day) versus 250 mg/day of desipramine (Norpramin), improvement in depression in those who responded to either SAM-e or desipramine correlated with their SAM-e blood levels (Bell et al., 1994).

"These findings highlight the need for larger and longer-term studies to elucidate the role of SAM-e in recovery from depression and the use of SAM-e in combination with prescription antidepressants," he said. He added that the longest controlled-trial studies of SAM-e efficacy for depression were 42 days (Delle Chiaie et al., 2000; De Vanna and Rigamonti, 1992; Fava et al., 1992).

Brown noted that American companies only sell SAM-e in 50 mg, 100 mg and 200 mg tablets. He recommended a daily dose of 400 mg for mild depression.

"Keep in mind that absorption is better on an empty stomach," he said. "Starting patients with 200 mg 30 minutes before breakfast and 30 minutes before lunch minimizes the overstimulation and insomnia which some patients report in the first few weeks. This can be switched to 400 mg before breakfast after a few weeks." Patients typically notice improvement in energy within two weeks.

Some investigators reported an overstimulation and/or insomnia rate of about 5%, which is the same as placebo (Berger and Nowak, 1987), according to Brown.

Brown continued, "As with most medications, clinical sense indicates starting with lower doses in geriatric, medically ill and anxious patients. SAM-e, like all antidepressants, should be used with some caution in patients with a history of cardiac arrhythmia."

He stressed that there have been surprisingly little data on the use of SAM-e in pregnancy and that the patient should "make a decision about SAM-e and pregnancy and lactation after discussing the pros and cons [with her doctor]."

SAM-e has been used to treat cholestasis of pregnancy in numerous studies with no adverse effects on mothers or children, Brown said. However, there are no definitive prospective long-term studies to exclude the possibility of teratogenic or neurodevelopmental effects (Brown et al., 2000). He added that since high levels of SAM-e are normal for infants, it is unlikely they would be harmed by the amount of SAM-e received through breast-feeding.

In several depression studies, SAM-e induced mania in a significant proportion of patients who had a prior history of bipolar disorder (De Vanna and Rigamonti, 1992; Kagan et al., 1990).

"As with any antidepressant medication, SAM-e can trigger hypomania or mania in patients with bipolar disorder," Brown warned, adding he would not recommend a patient with bipolar disorder take SAM-e unless that patient is under close medical supervision.

"If a patient has a personal or family history of bipolar disorder, lower starting doses of 100 mg once or twice a day, careful monitoring and concurrent use of mood stabilizers are indicated," Brown advised, adding "the dose can be raised by 200 mg to 400 mg every three to seven days."

Treatment for severe depression, Brown said, generally requires higher doses. "Some studies have started unipolar patients on 800 mg or 1600 mg per day," he said. Side effects occurring at the higher doses include mild jitteriness, loose bowels and headaches.

(To date, SAM-e has not been systematically studied in well-defined samples of psychotic or bipolar depressed patients-Ed.)

Brown noted that SAM-e is generally available in two forms: a butanedisulfonate form and a tosylate form.

"In my practice, the butanedisulfonate seems superior, particularly the enteric-coated form," he said, adding that good brands currently available in this country include Nature Made and GNC. "If a patient hasn't responded to an appropriate dose of SAM-e, the physician must be sure that the patient is using a potent brand."

"Only about 3% to 5% of patients discontinue SAM-e because of side effects, primarily gastrointestinal," Brown said. That is a relatively low rate compared to placebo discontinuation rates. In study after study, the investigators said there was no difference from placebo in the side effect rate."

The biggest study of SAM-e, Brown said, was a two-year postmarketing study of 20,641 patients conducted in Germany after SAM-e was approved for treatment of osteoarthritis (Berger and Nowak, 1987). "The investigators found that 80% of patients said they basically felt great on it and had no side effects, [while the other] 20% complained of mild side effects in the first month on high doses like 1200 mg/day to 1600 mg/day," Brown said.

At starting doses of 400 mg/day to 600 mg/day for mild depression, Brown said, there are no significant side effects. At higher doses, there are some "mild, temporary side effects."

Reports of drug interactions have been nearly nonexistent, according to Brown. He mentioned a case report of an elderly woman who was given clomipramine together with SAM-e. The patient exhibited symptoms of what the clinicians diagnosed as serotonin syndrome (Iruela et al., 1993). The investigators attributed it to a "toxic interaction produced by S-adenosylmethionine and clomipramine association."

Brown had some misgivings about the case report, however, explaining, "If you look at the world's literature of serotonin syndrome, the preponderance of cases are from clomipramine."

There have been no reports of SAM-e effects on cytochrome P450 metabolism or on the binding of prescription drugs to serum proteins (Brown et al., 2000).

Treatment-Resistant Depression

Research studies (Bell et al., 1994; Criconia et al., 1994; De Vanna and Rigamonti, 1992; Kagan et al., 1990) and his own clinical experience, Brown said, demonstrate that some patients have a dramatic response to SAM-e even after failing on prescription antidepressants. Brown described one of his patients who had been tried on all available antidepressants, including tricyclics (TCAs), serotonin reuptake inhibitors (SRIs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase (MAO) inhibitors, combinations of antidepressants and agents used to augment antidepressants, with little or no response.

"One week after beginning SAM-e, he showed significant improvement, which partially faded after several good months," said Brown. "We eventually added an SSRI to the SAM-e, even though previous trials of SSRIs had been ineffective. On this combination, the patient recovered...and has sustained remission on a reduced dose. When either SAM-e or the SSRI is decreased, depressive symptoms return."

Brown said he has treated more than 30 patients with treatment-resistant depression who responded well to SAM-e augmentation of all categories of antidepressants without adverse reactions, and noted a review of four studies suggesting that SAM-e boosted and hastened response to tricyclic antidepressants, mianserin and fenoterol, a ß-agonist (Friedel et al., 1989). He also cited a randomized double-blind study (Berlanga et al., 1992) of 40 outpatients with moderate to severe major depression that confirmed his own clinical experience of using SAM-e to augment imipramine.

Brown said he has also found SAM-e effective for fibromyalgia (Jacobsen et al., 1991; Tavoni et al, 1987, and Tavoni et al., 1998, as cited in Brown et al., 2000), depression in Parkinson's disease, the aging brain, liver diseases (Friedel et al., 1989) and arthritis (Bradley et al., 1994, as cited in Brown et al., 2000; Konig, 1987). It also seems to reverse some effects of alcoholic hepatitis and cirrhosis (Mato et al., 1999) and is used to dissolve gallstones. There is only one small open case series of SAM-e for attention-deficit/hyperactivity disorder (Shekim et al., 1990), but Brown mentioned that he has seen some anecdotal cases of his own (Brown et al., 2000).

"Preliminary studies support the use of SAM-e for depression complicating alcohol and opiate withdrawal" (Agricola et al., 1994), he said. "In several cases, we have used SAM-e to successfully treat post-methamphetamine depression and drug craving."

Brown said accumulated evidence indicates that SAM-e in higher doses is perhaps as effective for major depression as TCAs.

"SAM-e starts to work in approximately half the time needed for tricyclics. Studies show very few side effects, and SAM-e does not cause the sexual dysfunction or weight gain associated with other medications," he said.

Brown expressed concern about the need for most depressed patients to take antidepressants for long periods of time.

"Conventional medicine hasn't yet tackled the issue of long-term effects of prescription drugs," he said. "We hope they are insignificant, but there are no studies to assure us that these drugs are safe in the long-term. Part of our confidence derives from the clinical experience of prescribing tricyclics for over 35 years. Our experience with fluoxetine [Prozac] is only 12 years and with other SSRIs is even less."

Brown said that considering SAM-e's efficacy in treating depression, its mild side-effect profile, and its ability to boost antioxidants and protect DNA through methylation, this nutrient has advantages over prescription antidepressants.

Further Research Needed possible first-line treatment for affective disorders," Brown said. There have been about eight controlled studies comparing SAM-e in the oral version in decent doses from 1989 through 1997, Brown said, adding that a recently published review article describes the details of those studies (Brown et al., 2000).

"What everybody wants right now is a study comparing SAM-e to an SSRI," he said. "There are five studies showing that SAM-e boosts regular antidepressants [e.g., TCAs] in both their efficacy and speed of onset of therapeutic efficacy (Berlanga et al., 1992; Friedel et al., 1989; Torta et al., 1988). And we need more controlled studies showing that SAM-e can be a booster for other antidepressants...Those studies will probably get going in the United States within the next year or two."

He added that there is a planned study comparing the combination of SAM-e and an SSRI to an SRI alone, but it has not yet been funded.

"In the future, perhaps SAM-e will become available...as a prescription drug approved by the [U.S. Food and Drug Administration]," Brown said. "In the meantime, physicians should be knowledgeable about SAM-e in order to advise patients on its appropriate use as a complementary treatment or as an alternative to traditional pharmacotherapy."

REFERENCES

References

1. Agnoli A, Andreoli V, Casacchia M, Cerbo R (1976), Effect of S-adenosyl-L-methionine (SAMe)

upon depressive symptoms. J Psychiatr Res 13(1):43-54.
2. Agricola R, Dalla Verde G, Urani R et al. (1994), S-adenosyl-L-methionine in the treatment of major depression complicating chronic alcoholism. Current Therapeutic Research 55(1):83-92.
3. Andreoli VM, Maffei F, Tonon GC (1978), S-adenosyl-L-methionine (SAMe) blood levels in schizophrenia and depression. In: Transmethylations and the Central Nervous System, Andreoli WM, Agnoli A, Fazio C, eds. New York: Springer Verlag, pp147-150 [Italian].
4. Bell KM, Plon L, Bunney WE, Potkin SG (1988), S-adenosylmethionine treatment of depression: a controlled clinical trial. Am J Psychiatry 145(9):1110-1114.
5. Bell KM, Potkin SG, Carreon D, Plon L (1994), S-adenosylmethionine blood levels in major depression: changes with drug treatment. Acta Neurol Scand Suppl 154:15-18.
6. Berger R, Nowak H (1987), A new medical approach to the treatment of osteoarthritis.
7.Report of an open phase IV study with adementionine (Gumbaral). Am J Med 83(5A):84-88.
Berlanga C, Ortega-Soto HA, Ontiveros M, Senties H (1992), Efficacy of S-adenosyl-L-methionine in speeding the onset of action of imipramine. Psychiatry Res 44(3):257-262.
8. Bottiglieri T, Godfrey P, Flynn T et al. (1990), Cerebrospinal fluid S-adenosylmethionine in depression and dementia: effects of treatment with parenteral and oral S-adenosylmethionine. J Neurol Neurosurg Psychiatry 53(12):1096-1098.
9. Bottiglieri T, Hyland K, Reynolds EH (1994), The clinical potential of ademetionine (S-adenosylmethionine) in neurological disorders. Drugs 48(2):137-152.
10. Bressa GM (1994), S-adenosyl-L-methionine (SAMe) as antidepressant: meta-analysis of clinical studies. Acta Neurol Scand Suppl 154:7-14.
11. Brown RP, Gerbarg PL, Bottiglieri T (2000), S-adenosylmethionine in the clinical practice of psychiatry, neurology, and internal medicine. Clinical Practice of Alternative Medicine 1(4):230-241.
12. Brown R, Colman C, Bottiglieri T (1999), Stop Depression Now: SAM-e, the Breakthrough Supplement that Works as Well as Prescription Drugs in Half the Time…with No Side Effects. New York: Putnam Publishing Group.
13. Cantoni GL (1952), The nature of the active methyl donor formed enzymatically from L-methionine and adenosinetriphosphate. J Am Chem Soc 74:2942-2943.
14. Cerutti R, Sichel MP, Perin M et al. (1993), Psychological distress during puerperium: a novel therapeutic approach using S-adenosylmethionine. Current Therapeutic Research 53(6):707-716.
15. Crellin R, Bottiglieri T, Reynolds EH (1993), Folates and psychiatric disorders. Clinical potential. Drugs 45(5):623-636.
16. Criconia AM, Araquistain JM, Daffina N et al. (1994), Results of treatment with S-adenosyl-L-methionine in patients with major depression and internal illnesses. Current Therapeutic Research 55(6):666-674.
17. Curcio M, Catto E, Stramentinoli G, Algeri S (1978), Effect of S-adenosyl-L-methionine on serotonin metabolism in rat brain. Prog Neuropsychopharmacol 2(1):65-71.
18. Czyrak A, Rogoz Z, Skuza G et al. (1992), Antidepressant activity of S-adenosyl-L-methionine in mice and rats. J Basic Clin Physiol Pharmacol 3(1):1-17.
19. Delle Chiaie R, Boissard G (1997), Paper presented at the World Biological Psychiatry Congress [abstract 90-56], Biol Psychiatry 42:245S.
20. Delle Chiaie R, Pancheri P, Scapicchio P (2000), MC3: multicentre, controlled efficacy and safety trial of oral S-adenosyl-methionine (SAMe) vs. oral imipramine in the treatment of depression. Int J Neuropsychopharmacol 3(suppl 1):S230.**21.** De Vanna M, Rigamonti R (1992),

Oral S-adenosyl-L-methionine in depression. Current Therapeutic Research 52(3):478-485.
22. Fava M, Rosenbaum JF, Birnbaum R et al. (1992), The thyrotropin response to thyrotropin-releasing hormone as a predictor of response to treatment in depressed patients. Acta Psychiatr Scand 86(1):42-45.
23. Fava M, Rosenbaum JF, MacLaughlin R et al. (1990), Neuroendocrine effects of S-adenosyl-L-methionine, a novel putative antidepressant. J Psychiatr Res 24(2):177-184.
24. Friedel HA, Goa KL, Benfield P (1989), S-adenosyl-L-methionine. A review of its pharmacological properties and therapeutic potential in liver dysfunction and affective disorders in relation to its physiological role in cell metabolism. Drugs 38(3):389-416.
25. Iruela LM, Minguez L, Merino J, Monedero G (1993), Toxic interaction of S-adenosylmethionine and clomipramine. Am J Psychiatry 150(3):522 [letter].
26. Jacobsen S, Danneskiold-Samsoe B, Andersen RB (1991), Oral S-adenosylmethionine in primary fibromyalgia. Double-blind clinical evaluation. Scand J Rheumatol 20(4):294-302.
27. Janicak PG, Lipinski J, Davis JM et al. (1988), S-adenosylmethionine in depression. A literature review and preliminary report. Ala J Med Sci 25(3):306-313.
28. Kagan BL, Sultzer DL, Rosenlicht N, Gerner RH (1990), Oral S-adenosylmethionine in depression: a randomized, double-blind, placebo-controlled trial. Am J Psychiatry 147(5):591-595.
29. Konig B (1987), A long-term (two years) clinical trial with S-adenosylmethionine for the treatment of osteoarthritis. Am J Med 83(5A):89-94.
30. Losada ME, Rubio MC (1989), Acute effects of S-adenosyl-L-methionine on catecholaminergic central function. Eur J Pharmacol 163(2-3):353-356.
31. Mato JM, Camara J, Fernandez de Paz J et al. (1999), S-adenosylmethionine in alcoholic liver cirrhosis: a randomized, placebo-controlled, double-blind, multicenter clinical trial. J Hepatol 30(6):1081-1089.
32. Otero-Losada ME, Rubio MC (1989), Acute changes in 5-HT metabolism after S-adenosyl-L-methionine administration. Gen Pharmacol 20(4):403-406.
33. Rosenbaum JF, Fava M, Falk WE et al. (1990), The antidepressant potential of oral S-adenosyl-L-methionine. Acta Psychiatr Scand 81(5):432-436.
34. Salmaggi P, Bressa GM, Nicchia G et al. (1993), Double-blind, placebo-controlled study of S-adenosyl-L-methionine in depressed postmenopausal women. Psychother Psychosom 59(1):34-40.
35. Shekim WO, Antun F, Hanna GL et al. (1990), S-adenosyl-L-methionine (SAM) in adults with ADHD, RS: preliminary results from an open trial. Psychopharmacol Bull 26(2):249-253.
36. Torta R, Zanalda F, Rocca P et al. (1988), Inhibitory activity of S-adenosyl-L-methionine on serum gamma-glutamyl-transpeptidase increase induced by psychodrugs and anticonvulsants. Current Therapeutic Research 44:144-159.